REMARKS

Upon entry of this amendment, claims 1-7, 9, 11-17, 19-22, 24, and 26-32 will be pending. Claims 1-17 and 19-32 were pending. Claims 8, 10, 23, and 25 are cancelled without prejudice or disclaimer. No new claims have been added. Claims 1, 7, 9, 11, 14, 16, 17, 19, 22, 24, and 26-32 have been amended to more clearly define the claimed invention. Support for claims 1, 7, 9, 11, 14, 16, 17, 19, 22, 24, and 26-32 as amended may be found throughout the specification and in those claims as originally filed. Accordingly, no new matter is added by the amendments and entry thereof is respectfully requested.

In the response to election made on August 17, 2010, Applicants did not include claim 24 among those that read on the elected species. The Examiner noted that this appears to be in error. Applicants agree and thank the Examiner for careful review of the claims.

Rejections under 35 U.S.C. § 112, first paragraph (Written Description)

The Examiner rejected claims 1-9, 11-13, 17, 19-24, 26-28, and 32 under 35 U.S.C. § 112, first paragraph as allegedly lacking adequate written description. See Office Action at page 2. Specifically, the Examiner remarked that the specification "does not set forth any structural criteria to allow one to envision the genus of molecules that would in fact act via the claimed mechanism." Id at page 3. Applicants respectfully traverse.

Contrary to the Examiner's characterization, the specification describes structural criteria at length. The Background of the Invention discusses double stranded nucleic acids having different confirmations, as follows:

> Specifically, the deoxyribonucleotides within dsDNA form a southern $C_{2'}$-*endo* sugar conformation resulting in a B-form helical conformation, whereas ribonucleotides within dsRNA form a northern $C_{3'}$-*endo* pucker and an A-form helical geometry. In contrast, the deoxyribonucleotides of the RNA/DNA heteroduplex have been shown to adopt an eastern $O_{4'}$-*endo* sugar pucker resulting in a helical conformation where the RNA strand adopts A-form geometry and the DNA strand shares both the A- and B-form helical conformations.

Specification at pages 2-3. The specification explains that in certain circumstances, oligonucleotides having regions differently modified nucleosides are desirable. When certain such oligonucleotides hybridize to a target RNA, they form duplexes having regions of different conformations. For example, the specification describes gapmers that hybridize to RNA resulting in duplexes having A-form helices in the wings and a B-form helix in the gap. See Specification

at page 12. In certain such instances, it is desirable to include one or more transition moieties to reduce the conformational strain as the helix transitions from one conformation to the other. Transition moieties are "capable of modulating transfer of the helical conformation characteristic of an oligonucleotide bound to its 3'hydroxy to an oligonucleotide bound to its 5' hydroxyl, when the oligonucleotide is in a duplex with RNA." Id at page 12. Thus, the transition moiety is typically placed "at the junction of the regions, so as to impart a transition between the two regions of differing conformation." Id.

The Specification describes structures and characteristics that impart transition between two regions of differing conformation and provides a large number of examples. See for example, pages 13-14, 40-44, 95-96, 98-109, and 110-117. Certain transition moieties are flexible and/or have geometric conformations that are in between those of the two regions they are transitioning. See for example pages 95-96. The conformations of a many nucleosides are known or may be determined by one of ordinary skill. See for example, Saenger, W. (1984) *Principles of Nucleic Acid Structure*, Springer-Verlag, New York (cited at page 100 and incorporated by reference in the specification at page 117). Those conformations may be manipulated by modifying the sugar, base, and or linkage of a nucleoside, including, but not limited to, the large number of such modifications specifically provided and characterized in the present specification. Applicants submit that the transition moieties of the present claims are described and exemplified in the specification sufficient that one of skill in the art would appreciate that the inventors were in possession of the invention as claimed.

The Examiner further contends that the specification does not provide structural criteria to determine whether a modified base will form hydrogen bonds with target RNA and whether it will stack with adjacent bases. Applicants respectfully submit that one of ordinary skill can easily make such determinations based on the structure of the modified base and principles well known in the art.

Finally, the Examiner asserts that the specification fails to demonstrate that a nucleoside comprising tetrafluoroindolyl acts via the mechanism of claim 11. Applicants note that claim 11 does not recite a mechanism. Rather, it describes characteristics; that the base does not form hydrogen bonds with the target RNA and that it is capable of π stacking. Applicants submit that it is apparent to one of skill in the art that tetrafluoroindolyl possesses these characteristics based on its structure, which appears on page 110.

Applicants respectfully request reconsideration and withdrawal of the rejections based on 35 U.S.C. § 112.

Rejections under 35 U.S.C. §§ 102 and 103

Claims 1-7, 17, 19-22, and 32 were rejected under § 102 as allegedly anticipated by US 2003/0096770 to Krotz et al. (Krotz). Claims 1-9, 11, 12, 17, 19-24, 26, 27, and 32 were separately rejected as allegedly rendered obvious by Krotz. Since both rejections are based on Krotz and share the same deficiency they are addressed together.

The Examiner remarked that there "is a transitional moiety between the 2'O-methoxyethyl and deoxynucleotides that incorporates a 5-methylcytosine (see ISIS-9606, page 8, for example)." Office Action at page 4. Applicants agree that compound ISIS-9606 comprises a 2'-deoxynucleoside comprising a 5-methylcytosine nucleobase. However, that nucleoside is not a transition moiety as defined in the instant specification or claims.

As explained in the specification, "5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C (Sanghvi, Y.S., Crooke, S.T. and Lebleu, B., eds., *Antisense Research and Applications*, CRC Press, Boca Raton, **1993**, pp. 276-278) and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications." Specification at page 37. Further, the examples use 5-methylcytosine in both the control oligonucleotides and in those comprising a transition moiety. See, e.g., Example 8 at pages 114-115 testing the transition moiety 4-methyl-1H-Benzimidazole, using 5-methylcytosine in place of all cytosines throughout all oligonucleotides. A 5-methylcytosine nucleobase is a well characterized molecule that supports hydrogen bonding, is not capable of π stacking (note the absence of an aromatic ring), and does not modulate transfer of the helical conformation characteristic of an oligonucleotide. Accordingly, Krotz neither teaches nor suggests an oligonucleotide comprising the modifications recited in the rejected claims and, consequently, cannot anticipate nor render obvious the present claims. Applicants respectfully request reconsideration and withdrawal of the rejections based on 35 U.S.C. §§ 102 and 103.

CONCLUSION

Applicants submit that the present response is complete and complies with the requirements of 35 U.S.C. §121 and §372. In light of the above amendments and accompanying remarks, the Applicants respectfully request that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney at 858-314-1167 if a telephone call could help resolve any remaining items.

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Respectfully Submitted,
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